Remarks

Claims 154-168, 170-181, 211 and 212 are pending in the present application. In the Office Action of October 6, 2004, claims 154-168, 170-181, and 211 are rejected under 35 U.S.C. § 112. Claim 212 is allowed.

35 U.S.C. § 112

Independent claim 168 and claims 170-181 dependent thereon stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The rejection alleges that the claims contain subject matter which is not described in the specification in such a way as to enable one to make or use the invention.

Claim 168, as amended, is directed to a method of detecting the presence in a sample of at least one of first and second autoantibodies to an antigen. The method comprises contacting a mixture of the sample and antigen with a substrate having a first antibody immobilized thereon that binds to a first antigen binding site of the antigen, and a second non-immobilized antibody that binds to a second antigen binding site of the antigen.

In the absence of both the first and second autoantibodies, the antigen binds strongly to the first immobilized and the second non-immobilized antibodies without competition, yielding a strong signal. See, for example, Figures 9a, 9b, and 10a of the specification, and specifically step 6 with reference to these figures.

In the presence of a first autoantibody, binding competition with the first immobilized antibody for the antigen, as defined in claim 168 occurs, resulting in partial or complete inhibition in the antigen binding to the immobilized antibody thereby resulting in a reduced signal, or no signal being seen. See, for example, Figures 9a, 9b, and 10b of the specification, and specifically step 7 with reference to these figures.

In the presence of the second autoantibody, binding competition for the antigen with the second non-immobilized labeled antibody occurs as defined in claim 168. This competition partially or completely inhibits binding of the second non-immobilized

labeled antibody to the antigen, thereby leading to a reduced signal, or no signal being seen. This complete or partial inhibition is described with referenced Figures 9a, 9b, and 10b of the specification and specifically in steps 4 and 7 with reference to these figures.

In the presence of both first and second autoantibodies both the above described competition reactions can occur, again resulting in complete or partial inhibition of antigen binding to the first immobilized and second non-immobilized antibodies respectively and greater sensitivity (the effects of the first and second autoantibodies are additive). This is clearly described with reference to Figures 9a, 9b and 10b of the specification, and specifically in step 7 with reference to these Figures.

The rejection is based on an assertion that it should be possible to differentiate between the presence of first and second autoantibodies in the sample being screened. Applicants respectfully disagree. Differentiation of the first and second autoantibodies is not required in the method defined by claim 168. The purpose of the double-perturbation of antigen binding that is introduced by the presence of two separate autoantibodies to two binding epitopes of the antigen is to achieve increased sensitivity for the low concentration of autoantibodies characteristically present in a test sample. In support, we have amended the preamble of claim 168 to define a method of detecting in a sample of body fluid the presence of at least one of first and second autoantibodies to at least one antigen.

In the method of claim 168, competitive inhibition of binding to the first immobilized antibody or to the second non-immobilized antibody results in a reduced signal, or no signal being seen. Differentiation of the presence of the first and/or second autoantibodies in a disease sample is not intended by the claimed method. Claim 168 is directed to a method for detection based on a competition reaction of sufficient sensitivity that would enable the presence of autoantibodies in a sample of body fluid to be detected. In particular, the aim of the method as defined in claim 168 is to solve the problem of detecting in strip format autoantibody concentration in a test sample which is seen to be characteristically low as can often be the case when this low concentration of autoantibodies remains indicative or predictive of disease. Detection in strip format of a

low concentration of autoantibody in a test sample as is possible with the method of claim 168 provides a significant clinical advance to the art of autoantibody detection, enabling autoantibody detection with sufficient sensitivity to provide a reliable and meaningful diagnosis at the point of patient care.

The differentiation and identification of the respective first and second autoantibodies is not encompassed by a method as defined in claim 168. Claim 168 is amended to more accurately reflect this intention. The principles of the autoantibody/antigen/antibody binding occurring in the method of 168, as discussed above, are described throughout the specification and including, but not limited to page 13, line 17 through page 14, line 19; page 20, line 15 to page 22, line 3; descriptions for Figures 9a and 9b beginning on page 34, line 21 through page 37, line 13; and the example at pages 42 and 43.

Applicants assert that claims 168 and 170-181 dependent thereon are sufficiently described for use to detect either first or second autoantibodies without requiring undue experimentation. Consideration of the comments provided above and allowance of the claims are respectfully requested.

Independent claim 211 and claims 154-167 dependent thereon stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection. Claim 211 is directed to a method of screening a sample for distinct populations of first and second autoantibodies.

The rejection is based on the assertion that in the presence of either autoantibody one or autoantibody two, the antigen would only be allowed to bind to one location on the solid support, depending on which autoantibody was present to occupy the other binding site of the antigen. In this case, only one strong line of signal would be formed on the solid base. The rejection asserts that one would not be able to distinguish between the presence of one autoantibody or neither autoantibody or which autoantibody was present. Applicants respectfully disagree.

Claim 211 is clarified to indicate that the labeling means for detection are provided directly or indirectly to the antigen. This enables the presence of autoantibodies in the sample of body fluid to be detected as well as detection of antigen bound to either or both immobilized antibodies on the support.

In the presence of both the first and second autoantibodies, competition for binding of the antigen with both the first and second immobilized antibodies on the support results in partial or complete inhibition of antigen binding, thereby leading to reduced signal, or no signal being seen. See, for example, Figure 9d of the specification, and description of step 7 at page 36, line 25 through page 37, line 13.

In the absence of both the first and second autoantibodies, the antigen binds to both the first and second immobilized antibodies, without competition, resulting in two strong signals. This is specified in claim 211 as amended. Support is found in the specification at Figure 8a, noting the positions of the first and second immobilized antibodies (15a, 15b) respectively, with further description in step 4 at page 33, lines 5 through 11.

In the case where either the first or second autoantibody is present, one strong signal line is detected. More specifically, one strong signal line is detected at the location of the immobilized antibody which binds an antigen binding site to which there is no autoantibody in the sample, whereas at the position of the immobilized antibody which binds an antigen binding site to which there is an autoantibody in the sample, competitive binding is occurring due to the presence of autoantibody, and partial or complete inhibition of antigen binding is occurring, thereby leading to reduced signal, or no signal being seen. Since the location of each immobilized antibody is known, (see for example Figure 8a noting the positions of the immobilized antibodies 15a and 15b) the identity of the autoantibody detected or not detected is readily ascertained. Sufficient support is presented to allow one to use the claimed method to detect one autoantibody. Such support is found throughout the specification at Figures 8b, 8c and 8d, and specifically at steps 5, 6 and 7 with reference to these figures found at pages 33, line 13 through page 34, line 20.

Applicants respectfully assert that the method of 211, as amended, can be used to detect one, both, or the lack of first and second autoantibodies without undue experimentation. Consideration and allowance of claims 211 and 154-167 dependent thereon, are respectfully requested.

Allowance of the claims as earnestly solicited. If a Notice of Allowance is not forthcoming, the Examiner is encouraged to contact Anne M. Murphy, USPTO Reg. No. 55,327, at 612.371.5267 to schedule a telephone interview.

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